SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FLUPENE (Flucloxacillin Sodium for Injection BP 500 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Sterile Flucloxacillin Sodium BP
Equivalent to Flucloxacillin……500 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Flucloxacillin is indicated for the treatment of infections due to sensitive Gram-positive organisms, including β-lactamase-producing staphylococci and streptococci. Typical indications include:

Skin and soft tissue infections:

Boils, Cellulitis, Infected burns

Abscesses, Infected skin conditions, Protection for skin grafts

Carbuncles e.g. ulcer, eczema, and acne

Impetigo

Furunculosis, Infected wounds

Respiratory tract infections:

Pneumonia, Lung abscess,

Emphysema Sinusitis, Pharyngitis,

Otitis media and externa Tonsillitis,

Quinsy

Other infections caused by flucloxacillin-sensitive organisms:

Osteomyelitis, Urinary tract

infection Enteritis, Meningitis

Endocarditis, Septicaemia

Flucloxacillin is also indicated for use as a prophylactic agent during major surgical procedures when appropriate; for example cardiothoracic and orthopaedic surgery.

Parenteral usage is indicated where oral dosage is inappropriate.

4.2 Posology and method of administration

Posology

Depends on the age, weight and renal function of the patient, as well as the severity of the infection.

Usual adult dosage (including elderly patients)

Adults and adolescents over 12 years of age

Total daily dosage of 1 g - 6 g administered in 3-6 divided doses, by i.v. or i.m. injection.

In cases of severe infections: Up to 8 g per day administered in three to four infusions (over 20 to 30 min).

No intramuscular single bolus injection should exceed 2 g. The maximum dose of 12 g per day should not be exceeded.

Osteomyelitis, endocarditis - Up to 8 g daily, in divided doses six to eight hourly.

Surgical prophylaxis - 1 to 2 g IV at induction of anaesthesia followed by 500 mg six hourly IV, IM or orally for up to 72 hours.

Flucloxacillin may be administered by other routes in conjunction with systemic therapy. (Proportionately lower doses should be given in children.)

Intrapleural - 250 mg once daily.

By nebuliser - 125 to 250 mg four times a day.

Intra-articular - 250 to 500 mg once daily. Paediatric population

Premature infants, neonates, sucklings and infants:

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

Children under 12 years of age

25 to 50 mg/kg/24 hours administered in three to four equally divided doses by i.m. or i.v. injection.

In cases of severe infections: Up to 100 mg/kg/24 hours in three to

four divided doses. No single bolus injection or infusion should

exceed 33 mg/kg.

Children aged 10 to 14 years usually receive a daily dose of 1.5 g to 2 g and children aged 6 to 10 years 0.75 g to 1.5 g, divided into three to four equal doses.

Renal impairment:

In common with other penicillins, flucloxacillin usage in patients with renal impairment does not usually require dosage reduction. However, in the presence of severe renal failure (creatinine clearance < 10 ml/min) a reduction in dose or an extension of dose interval should be considered. The maximum recommended dose in adults is 1 g every 8 to 12 hours. Flucloxacillin is not significantly removed by dialysis and hence no supplementary dosages need to be administered either during, or at the end of the dialysis period.

Hepatic impairment

No dose reduction is necessary in patients with reduced

hepatic function. Method of administration

For instructions on preparation of the solutions for administration.

4.3 Contraindications

Hypersensitivity to the active substance or other β-lactam antibiotics (e.g. penicillins, cephalosporins).

Flucloxacillin is contra-indicated in patients with a previous history of flucloxacillin-associated jaundice/hepatic dysfunction.

Ocular or subconjunctival administration is contraindicated.

4.4 Special warnings and precautions for use

Before initiating therapy with flucloxacillin, careful enquiry should be made concerning previous hypersensitivity reactions to β-lactams. Cross-sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving β-lactam antibiotics. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral therapy. These reactions are more likely to occur in individuals with a history of β-lactam hypersensitivity.

If anaphylaxis occurs, flucloxacillin should be discontinued and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline (epinephrine). Ensure adequate airway and ventilation and give 100% oxygen. IV crystalloids, hydrocortisone, antihistamine and nebulised bronchodilators may also be required.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthematous pustulosis (AGEP). In case of AGEP diagnosis, flucloxacillin should be discontinued and any subsequent administration of flucloxacillin contra-indicated.

Flucloxacillin should be used with caution in patients with evidence of hepatic dysfunction, patients ≥ 50 years and those with serious underlying disease. In these patients, hepatic events may be severe, and in very rare circumstances, deaths have been reported.

Care is necessary if very high doses of flucloxacillin are given, especially if renal function is poor because of the risk of nephrotoxicity. Care is also necessary if large doses of sodium salts are given to patients with impaired renal function or heart failure.

Care is required when treating some patients with spirochaete infections such as syphilis or leptospirosis because the Jarisch- Herxheimer reaction may occur shortly after treatment with a penicillin is started.

Contact with flucloxacillin should be avoided since skin sensitisation may occur. Caution is advised in patients with porphyria.

Special caution is essential in the newborn because of the risk of hyperbilirubinaemia. Studies have shown that, at high dose following parenteral administration, flucloxacillin can displace bilirubin from plasma protein binding sites, and may therefore predispose to kernicterus in a jaundiced baby. In addition, special caution is essential in the newborn because of the potential for high serum levels of flucloxacillin due to a reduced rate of renal excretion.

During prolonged treatments (e.g. osteomyelitis, endocarditis), regular monitoring of hepatic and renal functions is recommended.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

In case of severe and persistent diarrhoea, the possibility of pseudomembranous colitis should be considered; flucloxacillin therapy should be discontinued.

There is evidence that the risk of flucloxacillin induced liver injury is increased in subjects carrying the HLA-B*5701 allele. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA- B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

Caution is advised when flucloxacillin is administered concomitantly with paracetamol due to the increased risk of high anion gap metabolic acidosis (HAGMA). Patients at high risk for HAGMA are in particular those with severe renal impairment, sepsis or malnutrition especially if the maximum daily doses of paracetamol are used.

After co-administration of flucloxacillin and paracetamol, a close monitoring is recommended in order to detect the appearance of acid–base disorders, namely HAGMA, including the search of urinary 5-oxoproline.

If flucloxacillin is continued after cessation of paracetamol, it is advisable to ensure that there are no signals of HAGMA, as there is a possibility of flucloxacillin maintaining the clinical picture of HAGMA.

This medicine contains approximately 26mg sodium per vial equivalent to 1.3% of the WHO recommended maximum daily intake of 2g sodium for an adult. This should be included in the daily allowance of patients on sodium restricted diets.

4.5 Interaction with other medicinal products and other forms of interaction

Other antibacterials:

Since bacteriostatic drugs such as chloramphenicol and tetracycline may interfere with the bactericidal effect of penicillins in the treatment of meningitis or in other situations in which a rapid bactericidal effect is necessary, it is best to avoid concurrent therapy.

Immunosuppressants:

There is reduced excretion of methotrexate (increased risk

of toxicity). Uricosuric agents:

Plasma concentrations of flucloxacillin are enhanced if probenecid is given

concurrently. Interference with diagnostic tests:

Penicillins may produce false-positive results with the direct antiglobulin (Coombs') test, falsely high urinary glucose results with the copper sulphate test and falsely high urinary protein results, but glucose enzymatic tests (e.g. Clinistix) and bromophenol blue tests (e.g. Multistix or Albustix) are not affected.

Paracetamol

Caution should be taken when flucloxacillin is used concomitantly with paracetamol as concurrent intake has been associated with high anion gap metabolic acidosis, especially in patients with risk factors.

4.6 Fertility, pregnancy and lactation

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of flucloxacillin on pregnancy or on the health of the foetus/new-born child. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women.

Breastfeeding

Flucloxacillin diffuses into breast milk in a limited amount and in rare cases this can lead to diarrhoea and/or fungal colonisation of the mucosa in the infant. The possibility of sensitisation of the infant to beta-lactam drugs should be considered.

Fertility

There are no data available on fertility.

4.7 Effects on ability to drive and use machines

Flucloxacillin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse reactions listed below are classified according to frequency and System Organ Class (SOC).

Very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Unless otherwise stated, the frequency of the adverse events has been derived from more than 30 years of post-marketing reports.

MedDRA System Organ Class	**Frequency**	**Undesirable Effects**
Blood and lymphatic system disorders	Very rare	Neutropenia (including agranulocytosis) and thrombocytopenia[1]. Eosinophilia. Haemolytic anaemia.
Immune system disorders	Very rare	Anaphylactic shock, angioneurotic oedema. If a hypersensitivity reaction occurs, the treatme should be discontinued. *(*See also *Skin a subcutaneous tissue disorders).*
Nervous system disorders	Very rare	In patients suffering from renal failure, neurological disorders with convulsions are possible with the I.V. injection of high doses.
Gastrointestinal disorders	Common[2]	Minor gastrointestinal disturbances
	Very rare	Pseudomembranous colitis[3.]
Metabolism and nutrition disorders	Very rare	Cases of high anion gap metabolic acidosis, wh flucloxacillin is used concomitantly wi paracetamol, generally in the presence of ri factors.
Hepato-biliary disorders	Very rare	Hepatitis and cholestatic jaundice. Changes in liver function laboratory test resul (reversible when treatment is discontinued). There is evidence that the risk of flucloxacill induced liver injury is increased in subjects carryi the HLA-B*5701 allele[5].
Skin and subcutaneous tissue disorders	Uncommon[2]	Rash, urticaria and purpura
	Very rare	Erythema multiforme, Stevens-Johnson syndrom and toxic epidermal necrolysis *(*See also *Immu system disorders)*
	Not known	AGEP - acute generalized exanthematous pustulosis
Musculoskeletal and connective tissue disorders	Very rare	Arthralgia and myalgia sometimes develop mo than 48 hours after the start of the treatment
Renal and urinary disorders	Very rare	Interstitial nephritis1
General disorders and administration site conditions	Very rare	Fever sometimes develops more than 48 hours after the start of the treatment

1. These are reversible when treatment is discontinued.

2. The incidence of these AEs was derived from clinical studies involving a total of approximately 929 adult and paediatric patients taking flucloxacillin.

3. If pseudomembranous colitis develops, flucloxacillin treatment should be discontinued and appropriate therapy, e.g. oral vancomycin should be initiated.

4. Hepatitis and cholestatic jaundice may be delayed for up to two months post-treatment. In some cases the course has been protracted and lasted for several months. Hepatic events may be severe, and in very rare circumstances, deaths have been reported. Most reports of deaths have been in patients > 50 years of age and in patients with serious underlying disease.

5. Despite this strong association, only 1 in 500-1000 carriers will develop liver injury. Consequently, the positive predictive value of testing the HLA-B*5701 allele for liver injury is very low (0.12%) and routine screening for this allele is not recommended.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via the Pharmacy and Poisons Reporting System (PVERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

Symptoms

Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident. With high parenteral doses of penicillins, neurotoxicity (e.g. convulsions, encephalopathy), blood disorders (e.g. neutropenia, haemolytic anaemia, prolongation of bleeding time, defective platelet function) or electrolyte disturbances may occur.

Treatment

Treatment is symptomatic.

Flucloxacillin is not removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Pharmacotherapeutic group: Antibacterials for systemic use, Beta-lactamase resistant penicillins

ATC code: J01CF05

Flucloxacillin is a semisynthetic penicillin (beta-lactam antibiotic; isoxazolylpenicillin) with a narrow spectrum of activity primarily against Gram-positive organisms, including β-lactamase- producing strains.

Mechanism of action

Flucloxacillin inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Mechanism of resistance

Resistance to isoxazolylpenicillins (so-called methicillin-resistance) is caused by the bacteria producing an altered penicillin binding protein. Cross resistance may occur in the beta-lactam group with other penicillins and cefalosporins. Methicillin-resistant staphylococci generally have low susceptibility for all beta-lactam antibiotics.

Antimicrobial activity

Flucloxacillin is active against both β-lactamase-positive and –negative strains of *Staphylococcus aureus* and other aerobic Gram-positive cocci, with the exception of *Enterococcus faecalis*. Gram positive anaerobes are generally susceptible (MIC 0.25-2 mg/l) but Gram-negative bacilli or anaerobes are moderately to fully resistant. Enterobacteria is fully resistant to flucloxacillin as well as methicillin-resistant staphylococci.

Strains of the following organisms are generally sensitive to the bactericidal action of flucloxacillin *in vitro*.

The minimal inhibitory concentrations (MIC) of flucloxacillin are quoted below:

Micro-organisms	**MIC (mg/l)**
Staphylococcus aureus	0.1 to 0.25
Staphylococcus aureus (beta-lactamase +)	0.25 to 0.5
Streptococcus pneumoniae	0.25
Streptococcus pyogenes (Group A beta-haemolytic) †	0.1
Streptococcus viridans group	0.5
Clostridium tetani	0.25
Clostridium welchii	0.25
Neisseria meningitidis	0.1
† The Group A beta-haemolytic streptococci are less sensitive to the isoxazolyl penicillins than to penicillin G or penicillin V.	

5.2 Pharmacokinetic properties

Absorption:

After the intramuscular administration of a single 250 or 500mg dose of flucloxacillin to volunteers, mean peak concentrations of the drug in serum were approximately 10.5 and 16mg.l-1 respectively. High serum levels of the drug are achieved when administered by intravenous bolus injection or by slow intravenous infusion: 30 minutes and 2 hours after a single 500mg intravenous bolus injection of flucloxacillin the mean serum concentration of the drug was 38 and 7.5mg.l-1, respectively; 30 minutes and 3 hours after a single 1g intravenous bolus injection of flucloxacillin, the mean serum concentrations

were 60 and 4mg.l- 1respectively. The administration of 2g flucloxacillin by intravenous infusion over 20 minutes resulted in mean serum concentrations of 244 and 27.7mg.l^{-1} 15 minutes and 120 minutes respectively after the end of the infusion.

Distribution:

Protein binding: The serum protein-binding rate is 95%.

Flucloxacillin diffuses well into most tissue. Specifically, active concentrations of flucloxacillin have been recovered in bones: 11.6 mg/l (compact bone) and 15.6 mg/l (spongy bone), with a mean serum level of 8.9 mg/l.

Crossing the meningeal barrier: Flucloxacillin diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed.

Crossing into mother's milk: Flucloxacillin is excreted in small quantities in

mother's milk. Biotransformation:

In normal subjects approximately 10% of the flucloxacillin administered is metabolised to penicilloic acid. The elimination half-life of flucloxacillin is in the order of 53 minutes.

Elimination:

Excretion occurs mainly through the kidney. Between 65.5% (oral route) and 76.1% (parenteral route) of the dose administered is recovered in unaltered active form in the urine within 8 hours. A small portion of the dose administered is excreted in the bile. The excretion of flucloxacillin is slowed in cases of renal failure.

Pharmacokinetic/pharmacodynamic relationship

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for flucloxacillin.

Neonates and infants

The clearance of flucloxacillin is considerably slower in neonates compared with adults and a mean elimination half life of approximately four and a half hours has been reported in neonates. Special care should be taken during administration of flucloxacillin to the newborn.

Younger infants (<6 months) achieve higher plasma concentrations of flucloxacillin than older children when given the same dose.

Patients with renal impairment

In patients with severe renal impairment the elimination half life of flucloxacillin increases to values of between 135-173 min. Modified dosage is required if renal impairment is severe, with creatinine clearance <10 ml/min.

Patients with hepatic impairment

Hepatic disease is thought unlikely to influence the pharmacokinetics of flucloxacillin as the antibiotic is cleared primarily via the renal route.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Not applicable.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section Special precautions for disposal and other handling.

Flucloxacillin should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

If flucloxacillin is prescribed concurrently with an aminoglycoside, the two antibiotics should not be mixed in the syringe, intravenous fluid container or giving set; precipitation may occur.

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Store below 30°C, and protect from light and moisture.

6.5 Nature and content of container

A 10 ml flint glass vial with dry sterile powder is packed in a Printed Primary Carton along with the Pack Insert.

6.6 Special precautions for disposal and other handling

Intravenous use:

Dissolve 250-500 mg in 5-10 ml Water for Injections. Administer by slow intravenous injection (three to four minutes).

Flucloxacillin may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Intramuscular use:

Add 2 ml Water for Injections to 500 mg vial contents. Intrapleural: Dissolve 250 mg in 5-10 ml Water for Injections.

Intrapleural: Dissolve 250 mg in 5-10 ml Water for Injections.

Intra-articular: Dissolve 250-500 mg in up to 5 ml Water for Injections or 0.5% lidocaine hydrochloride solution.

Nebuliser solution: Dissolve 125-250 mg of the vial contents in 3 ml sterile water.

Flucloxacillin 500 mg, Powder for Solution for Injection or Infusion has a displacement volume of approximately 0.35 ml when reconstituted as described above.

Flucloxacillin Injection may be added to the following infusion fluids: Water for Injections

Sodium chloride 0.9%

Glucose 5%

Sodium chloride 0.18% with glucose 4%.

7. MARKETING AUTHORISATION HOLDER

Market Authorisation Holder

Crown Healthcare

Address

CrownPlex, Mombasa Road,

Opp. JKIA Flyover, PO Box-40449-00100

Nairobi, Kenya

Country: Kenya

Manufacturer

Zazen Pharma Pvt. Ltd.

Address

Plot No. 7 & 8, National Highway

No. 8, Vasai Phata, Vasai (East),

Thane 401208 Maharashtra, India.

Country: India

8. MARKETING AUTHORISATION NUMBERS

CTD5145/14784

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of latest renewal: N/A

10. DATE OF REVISION OF THE TEXT

01/04/2026